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**(54) Title:** USE OF MACROLIDE COMPOUNDS FOR EYE DISEASES

**(57) Abstract**

Macrolide compounds such as the FR-900506 and its related compounds are provided for the prevention or treatment of eye diseases, particularly, allergic conjunctivitis. Composition containing such compounds is also disclosed.

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## USE OF MACROLIDE COMPOUNDS FOR EYE DISEASES

## DESCRIPTION

5 This invention relates to a new use of macrolide compounds for eye diseases. More specifically, this invention relates to a new use of macrolide compounds for eye diseases, particularly, allergic conjunctivitis.

10 Accordingly, this invention provides a new use of the macrolide compounds for preventing or treating eye diseases as mentioned above.

15 Further, this invention provides a prophylactic or therapeutic agent for eye diseases as mentioned above, which comprises the macrolide compounds.

20 Still further, this invention provides a method for preventing or treating eye diseases as mentioned above, which comprises administering said macrolide compounds to mammals.

25 Some of the macrolide compounds used in this invention are known and disclosed, for example, in European Patent Publication No. 0184162 and International Patent Application WO 89/05304.

30 Those known macrolide compounds include the fermentation products, such as FR-900506, FR-900520, FR-900523 and FR-900525, isolated from microorganisms belonging to genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 (FERM BP-927) or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 (FERM BP-928), and their related compounds prepared from these fermentation products. And new macrolide compounds can be prepared from the above known macrolide compounds in a conventional manner.

35 These macrolide compounds were indicated inter alia for use in the treatment of rejection to transplantation, autoimmune diseases and infectious diseases caused by pathogenic microorganisms, such as various fungi (Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, etc)(e.g. J. Antibiotics, XL(9), 1249-1255, 1987).

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The inventors of this invention have surprisingly found that the macrolide compounds mentioned hereinbelow are useful for preventing or treating eye diseases, particularly, allergic conjunctivitis, and also other allergic diseases such as food allergy, allergic rhinitis, etc.

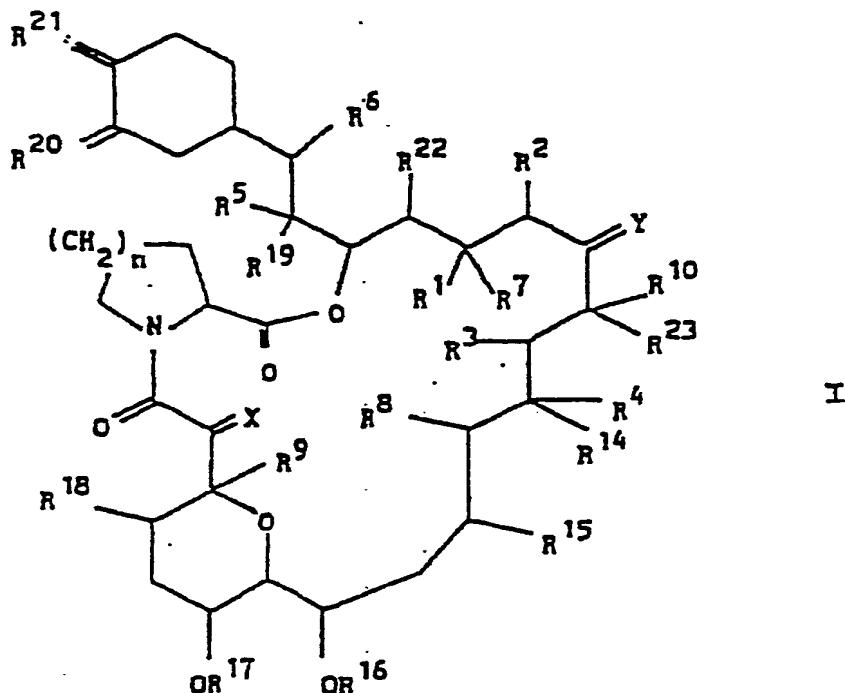
5 The macrolide compounds used in this invention can be represented by the following general formula (I).

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wherein each vicinal pair of substituents [ $R^1$  and  $R^2$ ], [ $R^3$  and  $R^4$ ], [ $R^5$  and  $R^6$ ] independently

a) represent two vicinal hydrogen atoms, or  
b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above,  $R^2$  may represent an alkyl group;

$R^7$  represents H, OH, protected hydroxy or O-alkyl, or in conjunction with  $R^1$  it may represent =O;

$R^8$  and  $R^9$  independently represent H or OH;

$R^{10}$  represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

X represents O, (H,OH), (H,H) or  $-\text{CH}_2\text{O}-$ ;

Y represents O, (H,OH), (H,H),  $\text{N}-\text{NR}^{11}\text{R}^{12}$  or  $\text{N}-\text{OR}^{13}$ ;

$R^{11}$  and  $R^{12}$  independently represent H, alkyl, aryl or tosyl;

$R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{22}$  and  $R^{23}$  independently represent H or alkyl;

$R^{20}$  and  $R^{21}$  independently represent O, or they may independently represent  $(\text{R}^{20}\text{a},\text{H})$  and  $(\text{R}^{21}\text{a},\text{H})$  respectively;  $\text{R}^{20}\text{a}$  and  $\text{R}^{21}\text{a}$  independently represent OH, O-alkyl or  $\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$  or  $\text{R}^{21}\text{a}$  is protected hydroxy;

in addition,  $\text{R}^{20}\text{a}$  and  $\text{R}^{21}\text{a}$  may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

in addition to their significances above, Y,  $\text{R}^{10}$  and  $\text{R}^{23}$ , together with the carbon atoms to which they are attached, may represent a 5- or 6- membered N-, S- or O-containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and  $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$ ;

and pharmaceutically acceptable derivatives thereof.

The specific examples of the definitions of compound (I) and the preferred working modes of the invention are described in detail below.

5 The term " lower " as used in this specification means, unless otherwise indicated, any number of carbon atoms between 1 and 6, inclusive.

10 Suitable " alkyl " means straight or branched saturated aliphatic hydrocarbon residue and may include lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, and the like.

15 Suitable " alkenyl " means straight or branched unsaturated aliphatic hydrocarbon residue having one double bond and may include lower alkenyl such as vinyl, propenyl, butenyl, methylpropenyl, pentenyl, hexenyl, and the like.

Suitable " aryl " may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like.

Suitable examples of the protective group in the " protected hydroxyl group " may include:

20 1-(lower alkylthio)(lower)alkyl groups such as lower alkylthiomethyl groups (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more desirably  $C_1-C_4$  alkylthiomethyl groups, and most desirably methylthiomethyl;

25 tri-substituted silyl groups such as tri(lower)-alkylsilyl groups (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl-dimethylsilyl, tri-tert-butyldimethylsilyl, etc.);

30 lower alkyl-diarylsilyl groups (e.g. methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyl-diphenylsilyl, etc.), more desirably tri( $C_1-C_4$ )alkylsilyl and  $C_1-C_4$  alkyldiphenylsilyl groups and most desirably tert-butyldimethylsilyl and tert-butyldiphenylsilyl; and

acyl groups such as aliphatic acyl groups, aromatic acyl groups and aliphatic acyl groups substituted by aromatic groups, which are derived from carboxylic acids, sulfonic acids or carbamic acids.

5        The aliphatic acyl group may include lower alkanoyl groups which may optionally have one or more suitable substituents such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, 10      carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkoxy-(lower)alkanoyl groups which may optionally have one or more appropriate substituents such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxy- 15      propionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl groups having one or more suitable substituents such as carboxy or protected carboxy, for example carboxy(lower)alkylcarbamoyl groups (e.g. 20      carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), protected carboxy(lower)alkylcarbamoyl groups such as tri(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl groups (e.g. trimethylsilylmethoxycarbonyl- 25      ethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so 30      on.

      The aromatic acyl group may include aroyl groups which may optionally have one or more suitable substituents such as nitro (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.),

5 arenesulfonyl groups which may optionally have one or more suitable substituent(s) such as halogen (e.g.

benzenesulfonyl, toluenesulfonyl, xenesulfonyl,  
naphthalenesulfonyl, fluorobenzenesulfonyl,

chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), and so on.

10 The aromatic group-substituted aliphatic acyl group may include ar(lower)alkanoyl groups which may optionally have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and so on.

15 Among the above-mentioned acyl groups, the more desirable acyl groups are  $C_1-C_4$  alkanoyl groups which may optionally be substituted by carboxy, cyclo( $C_5-C_6$ )alkyloxy- $(C_1-C_4)$  alkanoyl groups having two  $(C_1-C_4)$  alkyl groups in the cycloalkyl moiety, camphorsulfonyl, carboxy( $C_1-C_4$ )alkyl-carbamoyl groups, tri( $C_1-C_4$ )alkylsilyl( $C_1-C_4$ )alkoxycarbonyl- $(C_1-C_4)$  alkylcarbamoyl groups, benzoyl which may have one or two nitro groups, halogen-substituted benzenesulfonyl groups, phenyl( $C_1-C_4$ )alkanoyl groups having  $C_1-C_4$  alkoxy and trihalo( $C_1-C_4$ )alkyl groups. Of these groups, the most desirable are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

20 25 Suitable " 5- or 6-membered N-, S- or O-containing heterocyclic ring " may include pyrrolyl, tetrahydrofuryl, and the like.

30 Preferred embodiments of the Symbols  $R^1$  to  $R^{10}$ ,  $R^{14}$  to  $R^{23}$ , X, Y and n are as follows.

$R^1$  and  $R^2$  are each hydrogen or combined to form a second bond;

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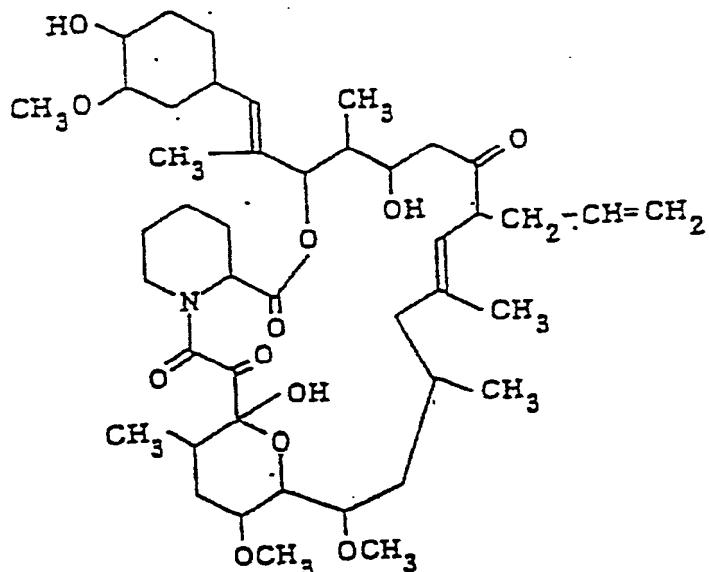
<sup>3</sup> and <sup>4</sup> are combined to form a second bond;  
<sup>5</sup> and <sup>6</sup> are combined to form a second bond;  
<sup>7</sup> is hydrogen, hydroxy, O-lower alkyl such as methoxy or protected hydroxy;  
5      <sup>8</sup> is hydrogen;  
      <sup>9</sup> is hydroxy;  
      <sup>10</sup> is methyl, ethyl, propyl or allyl;  
      <sup>14</sup>, <sup>15</sup>, <sup>16</sup>, <sup>17</sup>, <sup>18</sup> and <sup>19</sup> are each methyl;  
      <sup>20</sup> is oxo or [R<sup>20</sup>a,H], wherein R<sup>20</sup>a is hydroxy or  
10     methoxy;  
      <sup>21</sup> is [R<sup>21</sup>a,H], wherein R<sup>21</sup>a is hydroxy or protected hydroxy;  
      <sup>23</sup> is hydrogen;  
      X is oxo, (H,OH) or (H,H);  
15     Y is oxo; and  
      n is 1 or 2.

The pharmaceutically acceptable salt of the compound (I) is a nontoxic salt, which may be the corresponding salt with an inorganic or organic base such as alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), ammonium salt and amine salts (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and so on.

25     Referring to compound (I), there may exist conformers or one pair or more of stereoisomers such as optical and geometrical isomers due to the asymmetric carbon or the double bond. Such conformers and isomers also fall within the scope of the invention.

30     Particularly, the most interesting compound is FR-900506 of the following formula.

(continued to the next page)



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(hereinafter, described as FK506)

As example for showing pharmaceutical activity, the pharmacological test data of the macrolide compounds (I) is illustrated in the following.

Test : Effect of FK 506 on passive anaphylaxis in rat conjunctiva

25 The diluted rat antiserum (IgE) to ovalbumin in a  
volume of 50  $\mu$ l was injected into both palpebral  
conjunctivas of male Wistar/ST rats aged 6 weeks. Two days  
later, the rats were challenged intravenously with  
30 physiological saline (3ml/kg) containing 1% ovalbumin and  
0.5% Evans blue. The rats were sacrificed 30 min after  
challenge, and the eye tissues (eyelids and eyeballs) were  
removed. The intensity of anaphylactic reaction was assessed  
by measuring the amount of Evans blue extracted from the eye  
35 tissues.

Test drug (eye drop) prepared by Example 2 mentioned below was administered topically to the rats 5 and 15 min (Test 1), or 2, 4 and 6 hours (Test 2) before challenge. Control groups were similarly given vehicle. The effect of drug was expressed as percent inhibition of the optical density at 620 nm of the control groups. The result was expressed as the mean  $\pm$  S.E. and statistical analysis was performed by Dunnett's multiple comparison test.

Table : Effect of FK 506 on passive anaphylaxis in rat conjunctiva

Sample	Optical Density		Inhibition (%)
	Control	Test Sample	
Test 1	0.300 $\pm$ 0.035 (n=12)	0.116 $\pm$ 0.014 <sup>**</sup> (n=10)	61.4
Test 2	0.601 $\pm$ 0.047 (n=16)	0.177 $\pm$ 0.028 <sup>**</sup> (n=10)	70.5

\*\* :  $p < 0.01$

The macrolide compounds of the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the macrolide compounds of the present invention, as an

active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for 5 example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment and any other form suitable for use. The carriers which can be 10 used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing 15 preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

20 Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

25 For applying this composition to a human, it is preferable to apply it by external (topical) administration, particularly in the form of eye drops.

30 While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and more preferably 0.01-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally

administered. Daily doses for chronic administration in humans will be in the range of about 0.1-0.3 mg/kg/day.

The following examples are given for the purpose of illustrating the present invention.

5

Example 1

	FK 506	1 g
	Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
	Lactose	2 g
10	Croscarmellose sodium (Ac-Di-Sol)	1 g

The FK 506 (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. 15 Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK 506 (5 g). This composition was capsulated by a conventional manner to provide capsules containing 1 mg or 5 mg of FK 506 per each capsule.

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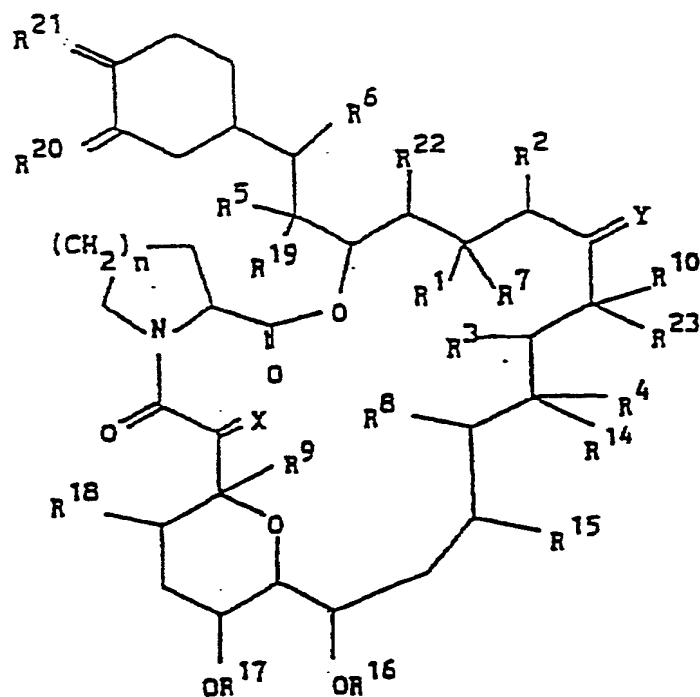
Example 2

	FK 506 (fine powder)	1 mg
	Polysorbate 80	0.5
	Polyvinyl alcohol	2.8
30	Benzalkonium chloride	0.1
	Sodium chloride	8.6
	pH5.25 Phosphate buffer	to 1 ml

An aqueous suspending eye drop containing the above-mentioned ingredients is prepared according to a conventional manner.

## CLAIMS

1. A use of macrolide compounds of the formula:



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wherein each vicinal pair of substituents [R<sup>1</sup> and R<sup>2</sup>], [R<sup>3</sup> and R<sup>4</sup>], [R<sup>5</sup> and R<sup>6</sup>] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached; in addition to its significance above, R<sup>2</sup> may represent an alkyl group;

R<sup>7</sup> represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R<sup>1</sup> it may represent =O;

$R^8$  and  $R^9$  independently represent H or OH;  
 $R^{10}$  represents H, alkyl, alkyl substituted by  
one or more hydroxyl groups, alkenyl,  
alkenyl substituted by one or more hydroxyl  
groups, or alkyl substituted by =O;  
5 X represents O, (H,OH), (H,H) or  $-\text{CH}_2\text{O}-$ ;  
Y represents O, (H,OH), (H,H), N-NR<sup>11</sup>R<sup>12</sup> or  
 $\text{N-OR}^{13}$ ;  
10 R<sup>11</sup> and R<sup>12</sup> independently represent H, alkyl,  
aryl or tosyl;  
R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>22</sup> and R<sup>23</sup>  
independently represent H or alkyl;  
15 R<sup>20</sup> and R<sup>21</sup> independently represent O, or they  
may independently represent ( $R^{20}\text{a},\text{H}$ ) and  
( $R^{21}\text{a},\text{H}$ ) respectively; R<sup>20</sup>a and R<sup>21</sup>a  
independently represent OH, O-alkyl or  
 $\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$  or R<sup>21</sup>a is protected  
hydroxy;  
20 in addition, R<sup>20</sup>a and R<sup>21</sup>a may together  
represent an oxygen atom in an epoxide ring;  
n is 1, 2 or 3;  
in addition to their significances above, Y, R<sup>10</sup>  
25 and R<sup>23</sup>, together with the carbon atoms to which  
they are attached, may represent a 5- or 6-  
membered N-, S- or O- containing heterocyclic  
ring, which may be saturated or unsaturated, and  
which may be substituted by one or more groups  
selected from alkyl, hydroxy, alkyl substituted  
by one or more hydroxyl groups, O-alkyl, benzyl  
30 and  $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$ ;  
or a pharmaceutically acceptable salt thereof, for  
preventing or treating allergic conjunctivitis.

2. A use of the macrolide compounds (I) defined in Claim 1

as a prophylactic or therapeutic agent for allergic conjunctivitis.

3. A prophylactic or therapeutic agent for allergic conjunctivitis, which comprises the macrolide compounds (I) defined in Claim 1.
4. A method for preventing or treating allergic conjunctivitis, which comprises administering the macrolide compounds (I) defined in claim 1 to mammals.
5. A use of the macrolide compounds (I) defined in claim 1 for manufacturing a medicament for preventing or treating allergic conjunctivitis.
6. A pharmaceutical composition for allergic conjunctivitis, which comprises the macrolide compounds (I) defined in Claim 1 in admixture with a carrier or excipient.
7. A process for preparing the pharmaceutical composition of Claim 6, which is characterized by admixing the macrolide compounds (I) with a carrier or excipient.
8. The macrolide compound used in Claims 1 to 7 is FK 506.
9. A use, prophylactic or therapeutic agent, method, pharmaceutical composition or process substantially as hereinbefore described as being in accordance with the present invention.

## INTERNATIONAL SEARCH REPORT

International Application

PCT/JP 92/00545

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1.5 A 61 K 31/71

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.C1.5	A 61 K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	Transplantation Proceedings, vol. 21, no. 1, February 1989, C. KOBAYASHI et al.: "Suppression of corneal graft rejection in rabbits by a new immunosuppressive agent, FK-506", pages 3156-3158 ---	
A	EP,A,0402931 (SANDOZ) 19 December 1990 ---	
A	WO,A,9009790 (BOEHRINGER) 7 September 1990 ---	
A	EP,A,0356399 (SANDOZ) 28 February 1990 ---	
A	EP,A,0184162 (FUJISAWA) 11 June 1986 (cited in the application) ---	-/-

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## IV. CERTIFICATION

Date of the Actual Completion of the International Search

11-06-1992

Date of Mailing of this International Search Report

21.07.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer



## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	WO,A,8905304 (FISONS) 15 June 1989 (cited in the application) -----	

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.

JP 9200545  
SA 58825

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/07/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0402931	19-12-90	AU-A-	5927790	08-01-91
		CA-A-	2032159	15-12-90
		WO-A-	9015805	27-12-90
		JP-T-	4500372	23-01-92
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WO-A- 9009790	07-09-90	DE-A-	3906214	30-08-90
		EP-A-	0485381	20-05-92
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EP-A- 0356399	28-02-90	AU-A-	4024689	01-03-90
		JP-A-	2167287	27-06-90
		US-A-	5011844	30-04-91
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EP-A- 0184162	11-06-86	AU-B-	592067	04-01-90
		AU-A-	5059685	12-06-86
		JP-B-	3046445	16-07-91
		JP-A-	3072483	27-03-91
		JP-A-	3072484	27-03-91
		JP-B-	3038276	10-06-91
		JP-A-	61148181	05-07-86
		US-A-	4956352	11-09-90
		US-A-	5110811	05-05-92
		US-A-	4894366	16-01-90
		US-A-	4929611	29-05-90
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WO-A- 8905304	15-06-89	AU-A-	2822889	05-07-89
		EP-A-	0323042	05-07-89
		EP-A-	0346427	20-12-89
		JP-T-	2502463	09-08-90
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